EXTENDED REPORT

Retinal findings in systemic sclerosis: a comparison with nailfold capillaroscopic patterns

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Objective: To determine the prevalence of retinal disease in systemic sclerosis (SSc) and to characterise the findings of retinopathy. Additionally, to analyse the association of retinal disease with other clinical/laboratory findings, particularly the findings of nailfold capillaries in patients with SSc.

Methods: Photographs of the ocular fundi were taken and were evaluated by an ophthalmologist who was unaware of the SSc status of the patients. The nailfold capillaries were analysed with a dermatoscope. Patients were divided into two groups according to the presence (group A) or absence (group B) of retinal disease.

Results: Retinal findings of the patients with SSc consisted of hard exudates, vascular tortuosity, microhaemorrhage, and macular degeneration. The prevalence of retinal disease among the patients with SSc was 34% (10/29), compared with 8%(3/38) among the controls (p=0.011). The mean systolic blood pressure and the age of the patients in group A were significantly higher than those in group B. However, there was no significant difference in the nailfold capillary damage between groups A and B.

Conclusion: Retinal abnormalities are often seen in patients with SSc and they may reflect the vascular changes characteristic of SSc. However, retinal changes may differ in quality from the changes of nailfold capillaries.

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterised by cutaneous and visceral fibrosis and proliferative intimal lesions of the small arteries, leading to an obliterative vasculopathy.[1] Although patients with SSc are known to have a variety of vascular abnormalities, retinal vascular damage is not well understood. Only a few published case reports have referred to occlusion of retinal arteries or veins in SSc.[2–5] Retinal vascular changes may reflect cerebral and sometimes general vascular changes.[6]

On the other hand, architectural abnormalities of the microvasculature, which are also characteristic of SSc, are easily visualised by wide field microscopy at the nailfold capillary bed. The nailfold changes in SSc include large dilated capillaries and extensive loss of capillaries.[7–10] The prevalence of each characteristic finding in SSc has been reported to be as follows: giant nailfold capillaries (43%), severe avascularity (44%), haemorrhage (35%).[11] To our knowledge, however, there have been no reports which refer to the association of the nailfold capillaries with visceral capillary findings. This prompted us to investigate the retinal vascular changes in patients with SSc and to analyse their association with the nailfold capillary changes.

PATIENTS AND METHODS

Patients and controls

We examined 29 patients (five male, 24 female) with SSc who fulfilled the American College of Rheumatology classification criteria for SSc.[12] Eight patients had diffuse and 21 limited type SSc. Thirty eight people who had a health check of their eyes were enrolled as controls; they were matched with the patients for age and sex. Table 1 summarises the age, sex, and other background measures of the patients and controls.

Ophthalmoscopic examination

An ophthalmologist (KU) evaluated the photographs taken by an ophthalmological camera (Canon CR5–45NM, non-attaching and non-mydriasis method) without knowledge of the SSc status of the patients.

Comparison of the patients with SSc with and without retinopathy

The patients with SSc were divided into two groups according to the retinal findings. Group A comprised patients with and group B patients without retinal disease. The groups were compared for their clinical background data.

Table 1 The background of the patients with SSc and controls. Mean (SD) values are shown

	Patients with SSc (n=29)	Controls (n=38)	p Value
Male/female	5/24	12/26	0.26
Age at ophthalmological examinations (years)	55.0 (11.6)	58.0 (11.5)	0.30
Age at onset of SSc (years)	46.3 (12.3)		
Disease duration (years)	13.5 (9.2)		
Systolic blood pressure (mm Hg)	120 (22)	126 (21)	0.29
Diastolic blood pressure (mm Hg)	74 (10)	76 (13)	0.45

Table 2 Incidence of retinal disease among the patients with SSc and controls. Results are shown as number (%)

Retinal disease	Patients with SSc (n=29)	Controls (n=38)
(+)	10* (34)	3 (8)
(–)	19 (66)	35 (92)

*p=0.011.

Table 3 Retinal abnormal findings in the patients with SSc

Patient number	Retinal findings					
	Hard exudate		Vascular tortuosity		Macular degeneration	
	Right	Left	Right	Left	Right	Left
1	X					
2			X	X		
3	X					
4	X	X				
5	X	X	X	X		
6			X			
7	X	X				
8						X
9			X	X		
10	X					

Examination of nailfold capillaries

The patients' nailfold capillaries were classified according to Cutolo *et al*.[13] The examination was carried out as follows: all digits in both hands were observed and photographs taken of the third and fourth digits of the hand that was most severely affected. We used an Olympus SZH-111 zoom-type microscope with 32–64-fold magnification. The nailfold capillaries were classified into three patterns as follows:

- Early pattern: few giant capillaries, few capillary haemorrhages, relatively well preserved capillary distribution, no evident loss of capillaries
- Active pattern: numerous giant capillaries, numerous capillary haemorrhages, moderate loss of capillaries with some avascular areas, mild disorganisation of the capillary architecture, absent or some ramified capillaries
- Late pattern: irregular enlargement of the capillaries, few or absent giant capillaries, absence of haemorrhages, severe loss of capillaries with large avascular areas, severe disorganisation of the normal capillary array, numerous ramified/bushy capillaries.

The retina and nailfold capillary findings in each patient were compared.

Statistical analysis

Student's *t* test and Fisher's exact test were used as statistical methods.

RESULTS

Prevalence of retinal disease in patients with SSc and controls

Ten of 29 (34%) patients with SSc had abnormal findings in the ocular fundi compared with 3/38 (8%) controls (p=0.011) (table 2). Table 3 summarises the retinal findings in the patients with SSc. They comprised hard exudates (nine eyes of six patients), vascular tortuosity (seven eyes of four patients), and macular degeneration (one eye of one patient). Figure 1 shows the ocular fundus of a patient with SSc. He had a hard exudate and small haemorrhages.

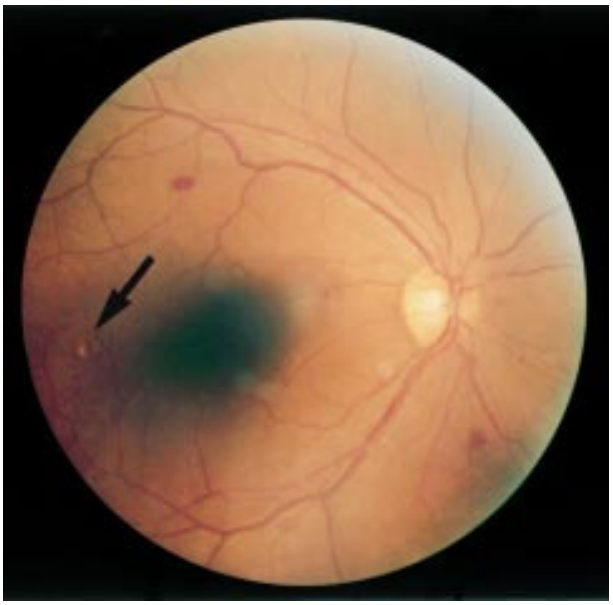

Figure 1 Sample of the retinal findings of a patient with SSc. He had hard exudates on his right ocular fundus (arrow).

Comparison of patients with retinal disease and those without

We compared the clinical and laboratory data of the patients in group A with those in group B (table 4). The mean (SD) systolic blood pressure at ophthalmological examination was significantly higher in group A than in group B (132 (21) mm Hg *v* 112 (19), p<0.03), but the former was not in the range of hypertension. Of the 10 patients of group A, only one patient was in a mild hypertensive state (150 mm Hg). Diastolic blood pressure in group A did not differ significantly from that in group B (77 (10) mm Hg *v* 72 (9) mm Hg, p>0.2). In addition, 2/10 (20%) patients in group A and 2/19 (11%) in group B were receiving antihypertensive drugs. The ratio of limited to diffuse type disease was similar (70.0% *v* 74%) in the groups. There was no significant difference in the incidence of Raynaud's phenomenon or of skin ulcers. No patient had renal failure. Other background factors did not show any significant difference. However, the patients of group A more frequently tended to have abnormal serological findings than those in group B. Thus antinuclear antibody (90% *v* 63%, p=0.26), anticentromere antibody (30% *v* 11%, p=0.21), and antitopoisomerase I antibody (50% *v* 35%, p=0.45) were more common in group A than in group B (not significant). Medical treatment, including prostaglandins (prostacyclin analogues—for example, alprostadil, beraprost sodium, cilostazol), D-penicillamine, and corticosteroids, did not differ between the groups (table 4).

Nailfold capillary findings and their relation to the retinal findings

We classified the changes of nailfold capillaries into three patterns. All patients examined had varying degrees of abnormality in the nailfold capillaries. Eight (80%) patients of group A and 17 (89%) of group B were examined for nailfold capillaries. Four (16%) of these 25 patients had an "early" pattern, 15 (60%) an "active" pattern, and six (24%) a "late" pattern. In group A, 1/8 (13%) patients had an early stage, 5/8 (63%) an active stage, and 2/8 (25%) a late stage pattern. Similarly, in group B, 3/17 (18%) patients had an early stage, 10/17 (59%) an active stage, and 4/17 (24%) patients a late stage pattern

Table 4 Comparison of clinical and laboratory data between two groups of patients with SSc. Results are shown as mean (SD) or as percentage

	Group A (positive retinal disease) (n=10)	Group B (negative retinal disease) (n=19)	p Value
Background			
Male/female	1/10	2/17	>0.5
Age at examination (years)	65.0 (5.7)	55.0 (12.1)	<0.03
Age at onset of SSc (years)	53.0 (10.0)	41.0 (14.0)	0.03
Disease duration (years)	13.2 (7.6)	13.9 (10.1)	0.85
General findings			
Disease type (limited/diffuse)	7/3	14/5	>0.5
(% limited type)	(70)	(74)	
Systolic BP (mm Hg)	132 (21)	112 (19)	0.03
Diastolic BP (mm Hg)	77 (10)	72 (9)	0.16
Raynaud's phenomenon	90	100	0.34
Skin ulcer	60	63	>0.5
Pulmonary fibrosis	30	58	>0.5
Laboratory data			
ESR (mm/1st h)	32 (23)	22 (20)	0.22
Antinuclear antibodies (+)	90	63	0.26
Rheumatoid factor (+)	60	52	>0.5
Anticentromere antibodies (+)	30	11	0.21
Antitopoisomerase I antibodies (+)	50	35	0.45
Anti-RNP antibodies (+)	0	6	>0.5
Drugs			
Prostaglandin*	50	47	>0.5
D-Penicillamine	100	90	>0.5
Corticosteroid	30	32	>0.5

BP, blood pressure; ESR, erythrocyte sedimentation rate;
*Prostaglandin: alprostadil or beraprost sodium or cilostazol.

Table 5 The retinal findings and changes of nailfold capillaries of the patients with SSc. Results are shown as the number of patients

		Changes of nailfold capillaries		
Group	Retinal disease	Early*	Active*	Late*
A	(+)	1	5	2
B	(–)	3	10	4

p>0.05
*See "Patients and methods, examination of nailfold capillaries" for classification of nailfold capillary patterns.

(table 5). No significant correlation was found between the nailfold capillary findings and those of the retinal vessels (table 5).

DISCUSSION

The pathophysiology of SSc is characterised by obstructive vascular lesions and proliferation of fibrous tissues and immunological abnormalities. Vascular lesions are reflected in manifestations such as Raynaud's phenomenon, cutaneous ulcer, and renal crisis with malignant hypertension.

In this study we showed that patients with SSc had a higher incidence of retinal changes associated with vascular damage than controls matched for age and sex. It is generally known that specific retinal lesions seen in SSc, such as cotton wool spots, intraretinal haemorrhage, and optic disc oedema, are most often caused by malignant hypertension.[14] However, the main retinal changes in our patients with SSc, most of whom were not hypertensive, included hard exudates and tortuous vessels. Ocular lesions associated with SSc have not been thoroughly investigated and, in particular, these retinal findings have not been described previously. Hard exudates are known to result from degeneration of neural elements, presumably caused by microvascular changes.[15] Tortuous changes of vessels may result from arteriosclerosis and thickening of the vessel wall.[15] Accordingly, the retinal changes found in this study may reflect vascular damage characteristic of SSc rather than hypertension because only one of our patients was hypertensive.

The incidence of retinal changes in patients with SSc was 34%, higher than that in patients with systemic lupus erythematosus as we have previously described.[16] Retinal lesions seen in the latter differ from those in the former, consisting mainly of cotton wool spots or haemorrhages and were related to the presence of antiphospholipid antibodies and central nervous system disease. The difference in the retinal findings between the two diseases may reflect the difference in features of vascular damage characteristic of each disease. Sulli *et al* showed that the most characteristic nailfold videocapillaroscopy pattern associated with antiphospholipid antibody positivity was the presence of linear haemorrhages or haemosiderin deposits with parallel deposition in the nailfold (comb-like haemorrhages).[17] Our patients who had abnormal retinal findings, however, did not show any evidence of antiphospholipid antibody syndrome.

Subdivision of patients with SSc into two groups according to the presence or absence of retinal changes did not disclose a prominent difference in clinical features except for ages and systolic blood pressure. It was shown that older age and higher systolic blood pressure were risk factors for vascular damage, at least in the retina, in patients with SSc, as is generally expected in normal subjects. On the other hand, other findings characteristic of SSc, like Raynaud's phenomenon, skin ulcer, and pulmonary fibrosis, were shown to have no specific correlation with retinal changes. Furthermore, retinal disease seems to be independent of the severity or extent of SSc because the type of the disease (limited/diffuse) and the method of treatment were similar in groups A and B. Interestingly, however, immunological abnormalities seem to be associated to some extent with retinal changes because group A patients tended to have a higher level of serum immunoglobulin, antinuclear antibodies, and anticentromere antibodies than group B, although the differences were not significant. The retinal changes may reflect a "vascular" phase of SSc which may result from certain immunological events. This remains to be investigated more extensively using larger samples.

The changes of nailfold capillaries are considered to reflect the stage of microangiopathy in SSc[13] and are easily observed

non-invasively. They consist of enlargement and tortuosity of individual capillary loops, haemorrhages, and capillary loop dropout, and may be caused mainly by the precapillary resistance associated with endothelial cell damage and structural changes of finger arteries seen in SSc.[18] Possibly, also, nailfold capillaries are affected by the tissue pressure of dermal swelling and sclerosis characteristic of SSc. To our knowledge, however, there have been no reports referring to a relationship between nailfold capillaries and retinal vessels, but, unexpectedly, our results showed little or no association between the two types of change. This indicates that the mechanisms involved in the damage of arteries and/or arterioles in the retina and damage of nailfold capillaries may differ. The retina is considered to be part of the brain and thus vascular damage in the retina may reflect, if not perfectly, damage in the brain. Cutolo *et al* have recently found focal or diffuse cerebral hypoperfusion in more than half of their neurologically asymptomatic patients with SSc as assessed by SPECT.[19] However, they attributed the low fibrosis in the brain to the absence of advanced vascular damage. Their results seem to support our finding, which showed no correlation between retinal and nailfold capillary changes. In comparison, changes of nailfold capillaries, which are caused by other factors, as mentioned above, may not necessarily express the systemic vascular changes.

In conclusion, it is now proved that the vascular disease characteristic of SSc is reflected considerably in the retina of patients with SSc. The presence of retinal changes should be combined with other findings to improve the diagnosis and to study progression of the disease. Examination of the ocular fundus is recommended for evaluation of vascular and other disease in patients with SSc.

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